Chapter 1

Hematopoietic Cell Transplantation for Autoimmune Diseases: A Review of History, Current State, and Future Issues

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http://dx.doi.org/10.5772/67604

Abstract

Autoimmune diseases are characterized by recurrent attacks and remissions, but as a rule they progress and eventually cause a severe disability and death. The present chapter contains general characteristics of autoimmune disease pathogenesis, ways to cause immune tolerance by hematopoietic cell transplantation (HCT), clinical aspects of the treatment for established autoimmune diseases with a special attention to multiple sclerosis (MS) and systemic sclerosis (SSc). A profound analysis of authors' point of view and of the available literature has been performed. The promising results allows to consider HCT as a relevant treatment option for a certain autoimmune diseases.

Keywords: hematopoiesis, autoimmune diseases, immunomodulation, hematopoietic cells

1. Introduction

Autoimmune disorders are affecting from 5 to 10% of the population. Usually, they are characterized by recurrent attacks and remissions, but as a rule they could develop with further progression and eventually development of a severe disability and death. The usual treatment of the vast majority of autoimmune diseases is immunosuppression. Newly proposed pharmacological agents can cause pronounce effect for the disease course and bring to a long-term remission. Evidences that certain autoimmune disorders can develop into a prolong treatment-free remission after hematopoietic cell transplantation (HCT) have been recently discussed in terms of human and animal models, including cases with accompanying

malignancies. The hypothesis that a strong immunosuppressive or myeloablative therapy can eliminate auto-reactive clones and cause a prolonged treatment-free remission is still open for analysis. It is still not clear whether myeloablative conditioning regimen with autologous HCT is more beneficial compared to a modern reduced intensity immune ablation with hematopoietic cell rescue. Other types of cell therapy are under intensive investigation at present too. Our present review will contain general characteristics of autoimmune disease pathogenesis, ways to cause immune tolerance (immunosuppression versus repertoire replacement), clinical aspects of HCT for established autoimmune diseases with a special attention to multiple sclerosis (MS) and systemic sclerosis (SSc), treatment regimens of autoimmune diseases and approaches for future therapies.

2. Back to immune tolerance: immunosuppression versus repertoire replacement and restoration of immune regulation

The treatment of autoimmune diseases, as pivotal goal, is to cause immune tolerance and therefore interrupt disease progression. The basic treatment of autoimmune disease is the immunosuppressive (and anti-inflammatory) therapy. In addition to different groups of cytotoxic immunosuppressive drugs, an increase in different types of monoclonal antibodies is seen. All they are directed to damage the number or function of lymphocytes. Immunomodulatory approaches are also in the center of research evaluation and clinical trial, performed with some indications to show effectiveness of this concept. For example, intravenous IgG therapy has major effects on idiotypic network immune regulation and demonstrates clinical effectiveness in many autoimmune diseases.

Thus, due to decreasing lymphocyte infiltration, cytokine production and secondary inflammatory changes, a repair of misbalanced immune regulation and pathogenic and networked anti-idiotypic antibodies can lead to interruption of inflammatory attack, slowing disease progression, prolong life expectancy and improve the quality of life of patients with autoimmune diseases. However, most if not all patients should stay lifelong on their treatment, and ultimately in addition to the disease itself, an accumulation of side effects brings them to irreversible deterioration.

The first modern fashion hematopoietic cell transplantation (HCT) was performed in 1967 by Gatti et al. [1], but a few approaches for allogeneic transplantation before MHC/HLA discovery were performed several years prior to them [2, 3]. If the aims of allogeneic HCT are the use of immune graft-versus-tumor effect or substitute the inborn or acquired error in hematopoiesis, the immunogenesis or metabolism will result accordingly. Autologous transplantations are performed with a goal to reach the highest tolerable level of cytotoxic antitumor effect saving hematopoietic system maximally intact and minimally impaired. The latter approach became standard of care for multiple myeloma and lymphomas, and in addition, it finds its place in some other malignancies (neuroblastoma, breast cancer, etc.).

Myeloablative conditioning with subsequent hematopoietic cells rescue (autologous transplantation) can re-establish the life-saving three lineage hematopoiesis, usually fast enough;

http://dx.doi.org/10.5772/67604

the white blood cells, the platelets, and the red blood cell engraftment occur in most of the cases within 2–3 weeks, registered in the vast majority of patients.

But while innate immunity usually restores in a few weeks, it takes much more time for recovery of adaptive immune system. In fact, despite a huge number of publications, there is no complex understanding concerning recovery of immunity after transplantation. What we exactly know is that this process is not simultaneous and that some segments of immune system can stay compromised for years. Those researchers, interested in specific details, can consider several resent reviews, but still majority of data are quantitative and fragmental [4].

Data concerning immune reconstitution after allogeneic HCT are dominating in medical literature. At the same time, there are less but still numerous publications and reviews concerning immune recovery after high-dose chemotherapy with hematopoietic cells rescue autologous transplantation. Again, there are many specific details that are reviewed elsewhere [5] but major conclusions could be briefly seen here.

Comparison of autologous and allogeneic HCT in terms of modification of immune system shows that auto-HCT, in general, causes less long and less deep disturbance of immune function. In case of allogeneic transplantation, the most important and significant factors are conditioning regimen (e.g., a myeloablative, MA or non-myeloablative stem cell transplantation, and NST), the use of serotherapy (e.g., antithymocyte globulin, ATG: more often late infections, more serious prevention of infections is necessary, etc.), graft manipulation (e.g., T repleted, T depleted and if depleted, then which way), prophylaxis, and treatment of developed graft-versus-host disease (GvHD) and procedures associated with the intensity and duration of immunosuppression.

Most of the mentioned factors are not existing in case of autologous transplantation by definition. Conditioning regimens in all standard cases of auto-HCT are myeloablative. They cause short-term deep aplasia and mucosa injury which eventually restore fast enough. More ancient phylogenetic defense mechanisms and cells, such as granulocytes, monocytes and NK cells, recover usually in 2–4 weeks. Lymphopenia normally stays longer and can be profound for a year after transplantation. But adaptive immune defense mechanisms does not expose to immunosuppressive medications, to circulating for several weeks antilymphocyte antibodies, GvHD (so-called autologous GvHD is more rare and much less severe and dangerous than GvHD after allogeneic transplantation), T cell depletion with need to rebuild acceptable quantity and repertoire of all lymphocyte subsets (except rare cases of graft purging by positive CD34+ selection), etc.

We can mention in advance that many of the rules of autologous transplantation are infringed in case of transplantation for autoimmune diseases; this will be discussed in details further in the text.

When immune reconstitution is discussed, the main attention goes to protection from infections and, in case of malignant diseases, to "graft-versus-tumor" effect. These factors shall govern and prevail treatment (transplant)-related mortality (TRM), overall survival (OS), and disease-free survival (DFS). Along with all that, there is one more aspect of immune

reconstitution and this is a reconstruction of self-tolerance [6]. In case of application of transplantation to autoimmune diseases, it becomes critical.

3. Concept

It is well established that the existing standard immunosuppressive/immunomodulating and anti-inflammatory treatment, even if prolonged, can lead to a remission, but the patient can never stay out of his or her medicamentous treatment and therefore cannot be defined as "cured." Moreover, lifelong therapy is clearly associated with side effects of prolonged use of immunosuppressors and/or anti-inflammatory drugs; a list of complication consists of a range of systems involvement, starting from gastrointestinal tract damage from nonsteroidal anti-inflammatory drugs and finishing with complex Cushing's syndrome due to steroids. Altogether, these complications tend to infections, cardiovascular problems, depression and social deprivation, and finally to a seriously compromised quality of life of these patients.

On the basis of this knowledge, the concept of total eradication of immune system, including auto-aggressive clones and auto-reactive immune memory with subsequent rebuilding of "normal" self-tolerant repertoire, looks extremely attractive. The concept of reconfiguration, "resetting" of immune system using HCT, has the aim "to cure," meaning to keep patient without disease progression and without any chronic disease-modifying antirheumatic drugs (DMARDs).

4. Background

Indeed and logically, there is enough background information to presume that HCT can be effective in autoimmune diseases according to our understanding of pathogenesis [7, 8].

Firstly, in the animal studies, a bulk of the experimental data is provided by models of syngeneic transplantations for adjuvant arthritis or collagen-induced arthritis (AA or CIA), for rheumatoid arthritis (RA) and experimental allergic encephalomyelitis (EAE) for multiple sclerosis (MS) on laboratory rodents [9]. It was clearly shown that the transplantation protects the cited conditions from relapse [10–12]. Similar effect was shown in autoimmune diseases with other target organs [13]. Re-induction with antigen after such transplantation did not provoke a relapse, and curative effect was shown in case of substitution of syngeneic transplantation with autologous one and with different conditioning regimens (some of them were shown as inadequate) [10, 14, 15]. This effect brought some investigators to the conclusion that at least some animal autoimmune diseases were stem cell diseases [16–18]. This still questionable opinion is in line with a few anecdotal observations of passive transfer of autoimmune diseases from the donor by allogeneic HCT; examples include insulin-dependent diabetes mellitus, former name for type 1 diabetes (T1D), mellitus and hypothyroidism [19], toxic diffuse goiter [20], myasthenia gravis [21], and multiple sclerosis [22, 23].

Our opinion, based on multiple published evidences that underestimation of specific local factors is incorrect, can be discussed. For example, transplantation performed in late stage of EAE leads to inferior outcomes [24]. Moreover, by monitoring of tracking of transplanted green fluorescent protein-transduced cells, the endogenous origin of microglia in advanced disease was shown. Host macrophages/microglial cells demonstrated robust activation and their number was higher in the stage of disease progression [25]. The same demonstration of different local trigger mechanisms can be made for systemic sclerosis (SSc), inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and other autoimmune diseases.

Secondly, before 1995, there were several cases or small series reports of coexistence of autoimmune diseases with other malignant conditions, which were the primary indication for HCT. After transplantation, the autoimmune diseases developed stable long-term remission, improvement of their symptoms, or alternatively proposed cure procedure. These cases included improvement or complete remission of RA by HCT for gold-induced aplastic anemia [26–28], full remission of psoriasis and ulcerative colitis [29], and resolution of autoimmune hepatitis after HCT for leukemia [30]. In addition, Nelson et al. [31] have reported 13 patients with either preexisting autoimmune diseases (11 patients), or diseases that are possibly autoimmune in nature (two patients), who underwent allogeneic HCT for the treatment of another pathology. None of these patients was found to have the autoimmune disease recurrence after HCT. However, there are other reports for patients whose RA have progressed [32] or had only a short period of relief from joint pain [33] following HCT.

5. Progress in transplantation for autoimmune diseases

The first report of HCT for autoimmune disease treatment as a primary indication was published in 1996 [57]. In the late 1990s of 20th century, a Joint Committee of the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT), joined by several North American and Australian centers, referred to as the International Autoimmune Disease Stem Cell Project, initiated a phase I/II study to assess feasibility, mortality, and preliminary response for this treatment model, performed for isolated autoimmune disease [34–36].

For over 20 years of experience, a reasonably big pool of clinical data of over thousands patients has been accumulated; this issue will be discussed in detail in the second half of this chapter. From the initial case reports, via small series and bigger retrospective group analysis, the studies came to phase II/III clinical trials. The concept of transplantation in autoimmune diseases itself has undergone a significant transformation. It looks naïve now, in terms of earlier views, when seriously discussed questions of syngeneic transplantations (which is casuistic), allogeneic transplantation (at present considered as too dangerous procedure for autoimmune disease, as potentially having incapacitating consequences, like GvHD) or absolutely indicated autoimmune transplantations (considered like panacea), were discussed [37].

5.1. So, what was changed?

Initially, and this is still the dominant dogma, that transplantation is considered exclusively as prolonged immune suppression with rebuilding de novo immunopoiesis and therefore a tolerance. But comprehension is coming that this is only one side of the immune "resetting" and HCT is not a simple immunosuppression. Reinfusion of hematopoietic stem cells after severe immunoablative causes regeneration of a new naïve immune repertoire from the patient's thymus [38]. Moreover, autologous HCT probably causes restoration of immune regulation and abnormal FoxP3 function of CD4+CD25+ (Treg) cells, as one of the main pathogenic mechanism of many autoimmune diseases [24, 39].

Gradually but persistently, conditioning regimens tend to undergo certain changes. In the first report of EULAR/EBMT, Tyndall (1999) [36] listed four main conditioning regimens that were used: (i) BEAM polychemotherapy (BCNU, VP-16, Ara-C, and melphalan) ± antithymocyte globulin (ATG), (ii) CyATG, consisted of 200 mg/kg of cyclophosphamide (Cy) ± ATG, sometimes substituted with monoclonal antibodies, usually Campath (alemtuzumab, antibody targeted CD52-expressing cells: lymphocytes, monocytes and dendritic cells), (iii) busulfan and cyclophosphamide (BuCy), and (iv) Cy and total body irradiation, usually 8 Gy (CyTBI) ± ATG. BEAM-ATG till nowadays keeps its role as a central conditioning protocol despite the fact that it causes high rate of side effects, including life-threatening ones [40]. Non-myeloablative protocols based on maximal dose of cyclophosphamide demonstrate probably similar effectiveness with impression of lower toxicity [41, 42]. Other procedures of different reduced toxicity of immunoablative but not always myeloablative conditioning were published as well: mini BEAM-like, BCNU/CCNU with intermediate dose of melphalan, ±ATG or alemtuzumab, rituximab, or Cy ± thiotepa or fludarabine, etc. Some could lead to the possibility of performing this procedure in outpatient manner [43–45].

Accompanying additional therapy is also improving during the entire period of analysis.

In other words, all discussed progressively resulting models developed different philosophy of autologous transplantations for autoimmune diseases, compared to other types of autotransplants (possibility to use non-myeloablative but immunoablative regimens, wide use of antilymphocyte antibodies, potential for reduction of toxicity, etc.). The critical advance of this evolution brings to major reduction of TRM from 20 to 30% up to very close to 0%. This is especially important when referred to application of HCT with early stages of slow progressive diseases with life expectancy of dozens of years.

6. Potential effectiveness of HCT for specific diseases

HCT was reportedly applied to 2–3 thousands patients worldwide, and since 2010, the yearly number of HCT procedures registered has increased by 30%, reflecting a change in practice [46]. Despite major basic similarities between different nosology entities, neither data reliability nor even experience with hematopoietic cells transplantation was considered uniform. Therefore, quite a few specific details should be overviewed to make picture certain. Some diseases are

prevalent while some are rare; some can be long time controlled with minimal and available measures while some characterized with fast progression of severe disability and dramatically shortened life expectancy. Altogether, this heterogeneous group of conditions, affecting 8–10% of the population [47], but at present only for several forms of HCT, can be considered as an optional or investigational treatment. Phase I/II studies and then randomized trials have been designed for SSc, MS, IBD, RA, and chronic inflammatory demyelinating polyneuropathy (CIDP).

6.1. HCT for systemic sclerosis

SSc is a relatively rare connective tissue disease (prevalence ranged from 7 to 489 cases per million individuals [48]). It is characterized by early vasculopathy, autoantibody formation, low-grade inflammation, enhanced collagen synthesis, and fibrosis in skin and internal organs. Autoimmunity is triggered by antigens and has some genetic background, associated with loci at HLA-DPB1 and HLA-DPB2 [49], and several polymorphisms of other genes involved in immune regulation, including BANK1, C8orf13-BLK, IL-23R, IRF5, STAT4, TBX21, and TNFSF4 [50]. Both T and B lymphocytes are involved in the immune process, and it is accompanied by profibrotic cytokine production, such as transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF), as well as fibroblast activation. It is interesting that many of the polymorphisms associated with SSc are shared with systemic lupus erythematosus (SLE) and other autoimmune diseases; they reflect on their pathophysiological importance, but not for SSc as a separate nosology. Polymorphisms that have failed to be confirmed in follow-up studies include TGF-β and CTGF [51]. In the Caucasian cohorts, the associations were significant for SSc patients with either antitopoisomerase-1 or anticentromere autoantibodies [50].

SSc is clinically characterized by extensive involvement of skin and visceral organs. For skin assessment, the modified Rodnan's skin score (mRSS) is used: a semi-quantitative skin thickness evaluation in 17 different body areas. Upon the degree of skin involvement, extended and limited SSc are differentiated. The extensive skin damage, associated with a degree of visceral organs involvement and the presence of heart, lung or renal disease, can increase the 5 year mortality rate up to 40–50% [52–56].

In terms of such serious prognosis, SSc was one of the first reported cases of autoimmune disease where HCT was applied [57]. Since then, most of numerous small case series and phase I/II studies and three randomized trials demonstrated encouraging data.

The two randomized studies are described in detail and discussed in the present study: ASSIST performed by USA Chicago group [58]: a phase II study, including 19 patients, aged younger than 60 years, with diffuse SSc, mRSS of 14 or more, and internal organ involvement or restricted skin involvement (mRSS < 14), but coexistent pulmonary involvement. The patients were randomly allocated in two equal groups to receive HCT (n = 10) or to receive 1 g/m^2 intravenous cyclophosphamide once per month for a period of 6 months (n = 9). The conditioning was non-myeloablative of intermediate toxicity, and consisted of 200 mg/kg intravenous cyclophosphamide and 6.5 mg/kg rabbit ATG, CyATG protocol. All 10 patients,

who received HCT, had no disease progression, and all 10 improved at or before 12 month follow-up, compared with none of nine treated with monthly cyclophosphamide (odds ratio 110, 95% CI 14.04–∞; p = 0.00001); eight of these nine controls had disease progression (p = 0.0001 versus HCT group), and 7 patients switched to HCT.

ASTIS [42] is an EBMT/EULAR phase III, multicenter, randomized, open-label, and parallel-group clinical trial, conducted at 29 centers of 10 European countries. It included 156 patients between 18 and 65 years of age with mRSS 15, with disease duration of 4 years and involvement of heart, lungs, or kidneys. In addition, inclusion of patients was allowed with disease duration of 2 years or less, and no major organ dysfunction as defined above provided they had an mRSS of ≥20 and an erythrocyte sedimentation rate greater than 25 mm/h and/or hemoglobin less than 11 g/DL, not explained by causes other than active scleroderma. Patients were randomly assigned to receive HCT (n = 79) or cyclophosphamide (n = 77). The CyATG conditioning regimen was very similar to Chicago study (total cyclophosphamide 200 mg/kg and intravenous rabbit ATG (Genzyme) in a total dose of 7.5 mg/kg). The dose of cyclophosphamide in the control group was 750 mg/m^2, repeated in 12 monthly pulses. During the first year, there were more irreversible events with organ failure or death in the HCT group, 13 (16.5%) versus 8 (10.4%) in the cyclophosphamide group. However, during the second year, the cumulative events were similar in both groups: 14 (17.7%) versus 14 (18.2%). And by the 4-th year, the cumulative events in HCT group 15 (19%) were less than cyclophosphamide group 20 (26%).

At present, one more phase III clinical trial scleroderma: cyclophosphamide or transplantation (SCOT) [59] is completed but the results are not published yet. The SCOT protocol employs a lymphoablative preparative regimen, including 800 cGy TBI, delivered in two 200 cGy fractions twice a day before CD34+ selected autologous hematopoietic stem cell transplantation [60]. The late results will be especially important to evaluate appearance of secondary malignancies in association with the radiotherapy.

Therefore, employment of HCT has resulted in rapid and sustained improvement of skin thickening and functional ability, stabilization of major organ function with some improvement of vital capacity in pilot studies, registry analyses, and the phase II–III trials. Some patients have achieved complete remission (CR) including unexpected and dramatic clinical and biopsy regression of dermal fibrosis as well as normalization of the microvasculature [61].

Despite an early treatment-related mortality rate of around 6–10%, potential long-term complications and an increase in serious adverse events, HCT conferred a long-term survival benefit.

6.2. HCT for multiple sclerosis

In MS, a chronic inflammation of the central nervous system (CNS) is caused by an autoimmune reactivity of T cells toward CNS myelin components and therefore has classical autoimmune nature [62].

Primary susceptibility to MS in the majority of various populations is associated with HLA-DrB1*15 [63, 64]. Recent genome-wide association studies (GWAS) identified multiple loci

http://dx.doi.org/10.5772/67604

affecting the risk of developing disease. The reported screen implicates a majority of these genes as immune related and coding for cytokine pathway (CXCR5, IL2RA, IL7R, IL7, IL12RB1, IL22RA2, IL12A, IL12B, IRF8, TNFRSF1A, TNFRSF14, TNFSF14), co-stimulatory (CD37, CD40, CD58, CD80, CD86, CLECL1) and signal transduction (CBLB, GPR65, MALT1, RGS1, STAT3, TAGAP, TYK2) molecules. In addition, some other genes are related to previously reported environmental risk factors such as vitamin D—CYP27B1, CYP24A1 and therapies for multiple sclerosis including natalizumab—VCAM1 and daclizumab—IL2RA [65].

At present, four different clinical patterns of MS are considered: clinically isolated syndromes (CIS; the first attack of a disease compatible with MS), relapsing-remitting MS (RRMS; clearly defined relapses without or with minimal residual deficit upon recovery), secondary progressive MS (SPMS, as a result of conversion of RRMS with or without occasional relapses and with gradual worsening), and primary progressive MS (PPMS, accumulation of disability from the very beginning of the disease and worse prognosis compare to RRMS/SPMS). The term progressive-relapsing multiple sclerosis (PRMS) is now obsolete [66].

The most commonly used rating scale to grade neurological disability in patients with MS is the expanded disability status scale (EDSS) [67].

Magnetic resonance imaging (MRI) is sensitive to focal CNS lesions and has been included in the diagnostic workup of patients in whom MS is suspected. Conventional MRI measures of the disease burden are useful tool to monitor the disease course.

Over the years, therapeutic approaches to MS were aimed at suppressing the immune system, in order to control the inflammatory process which causes the demyelination and finally irreversible axonal damage [68, 69].

The long list of registered therapies for MS includes corticosteroids (used mainly in a high-dose fore acute attack), immunosuppressive and immunomodulatory drugs (such as gilenya, teriflunomide, dimethyl fumarate, etc.), cytokines (interferons, IFN-alpha and IFN-beta), and strong immunosuppressive modalities (alemtuzumab, natalizumab, mitoxantrone, and cyclophosphamide). In many cases, registered disease-modifying treatments do not provide satisfactory control of MS due to their inability to eradicate the self-specific T-cell clones and compartmentized inflammation *in situ*, which is less affected by the conventional modalities and seems to be the reason for lack of efficacy of any of the registered treatment models in the progressive phase of MS. That is why the best available conventional therapy has only partial beneficial effects [64, 70, 71].

According to the recent published databases from Europe, North America, and South America, multiple sclerosis (followed by SSc) is constantly the most common indication for HCT [48, 72, 73].

The pioneer publication of Fassas et al. [74] described a phase I/II study, involving 15 patients with progressive median EDSS of 6 (5–7.5). The patients were treated with BEAM protocol followed by autologous HCT and antithymocyte globulin (ATG). Results were encouraging: short time (6–18 months) neurologic improvements have been detected using EDSS in 7 of 15 patients, and what was more obvious, using Scripps Neurologic Rating Scale (SNRS), which is more sensitive but not based predominantly on walking ability. One patient worsened

after 3 months and two have relapsed. There were no toxic deaths and reasonable number of side effects, mainly due to ATG infusion and infections during neutropenia. Since that time, BEAM-ATG became a gold standard for future trials and in use until nowadays.

The BEAM-ATG demonstrates its effectiveness in several trials, including the most recent ones.

The autologous hematopoietic stem cell transplantation trial in MS (ASTIMS) is promoted by the EBMT multicenter, randomized trial. Initiated as phase III study, it was transformed to phase II with a primary laboratory endpoint [40]. The aim was to compare BEAM-ATG with mitoxantrone 20 mg monthly for 6 months. The including criteria were SPMS or RRMS, with an increase of the EDSS in the last year, despite conventional therapy, and the presence of one or more active gadolinium-enhancing areas on MRI. Twenty-one recruited patients were randomized in either HCT (n = 9) or mitoxantrone (n = 12) arm. All but two patients were followed up for 4 years. The relapse rate was reduced in patients treated with HCT, when compared with mitoxantrone. HCT significantly reduced by 79% of the number of new T2 lesions compared to mitoxantrone (median number 2.5 versus 8). In the AHCT group, no new gadolinium-enhancing lesions appeared on brain MRI, while 56% of patients treated with mitoxantrone presented at least one active lesion. Despite the fact that there was no treatment-related mortality, serious adverse events (SAEs) were seen only in HCT arm. They were defined as life threatening in 2 patients at least. There were no deaths or late SAE. Adverse events were resolved without sequelae.

Another significant report was published by Burt's group [75] and it includes a single institution (Chicago, USA), experienced with treatment of 145 patients with RRMS (n = 123), or treated on a compassionate basis SPMS (n = 28), and with a median follow-up of 2 years. The main group consisted of patients aged 18–55 years, and their including criteria were RRMS. The therapy was unsuccessful with ≥1 conventional drug, EDSS from 2.0 to 6.0, and during the preceding year, the patients had either ≥2 relapses or 1 relapse treated with a corticosteroid and additional gadolinium-enhanced lesions on MRI scan at a separate time.

The conditioning regimen consisted of 200 mg/kg of cyclophosphamide divided into four single daily doses, plus either 20 mg of alemtuzumab given 2 days before stem cell infusion (22 patients) or 6 mg/kg of ATG (thymoglobulin), divided into five daily doses (129 patients).

Prior to each antithymocyte globulin infusion, additionally 1 g of methylprednisolone was infused.

There was a significant improvement in disability defined as decrease in EDSS score of ≥1.0, with proportion of patients 50% (95% CI, 39–61%) in 41 of 82 for improvement at 2 years and 64% (95% CI, 46–79%) in 23 of 36 for improvement at 4 years. The authors found a significant decrease of T2 lesion volume. Several other evaluated scores demonstrated pronounced and statistically significant improvement including notable advance in total quality of life scores. Treatment-related mortality was 0% and overall survival was 99.3%; the only death that occurred 30 months after transplantation was due to cardiovascular disease.

Hamerschlak et al. [76] performed a direct comparison of BEAM-ATG and CyATG regimens in a prospective multicentric Brazilian MS trial. The authors found that the rate of compli-

cations during transplantation was higher in the BEAM-ATG group (71.4%), compared to the CyATG group (40%; $p < 0.04$). Three subjects (7.5%) died of cardiac toxicity, sepsis, and alveolar hemorrhage, all of them from the BEAM-ATG group. The important conclusion was that despite the lower toxicity of CyATG, this regimen seems to be associated with the same outcome, but with lower toxicity, compared to BEAM-ATG.

Summarizing the cited protocols, with domination of BEAM and Cy (200 mg/kg), both ±ATG/alemtuzumab make an impression that in case of MS, lower intensity protocols demonstrate lower, up to 0%, mortality rate, while OS and progression-free survival are similar; in resent studies, they range from 65 to 100%, far better than the results of conventional MS therapies [77–81]. Our limited experience demonstrates 71% of progression-free survival after non-myeloablative transplantations performed in Hadassah-HUJI Medical Center (14 patients, 1998–2016, 12 after autologous and 2 after allogeneic transplantation; S. Savin, R. Or, M. Shapira and I. Resnick; unpublished data).

The risk of treatment-related mortality in HCT conventionally perceived to be unacceptably high. In a similar approach, the vein statistical analysis demonstrates a decrease in TRM to 1.3%, according to an analysis of the EBMT registry [82], and 0% in the most recent published profound enough series. The major role resulting from the studies is the development and choosing of less toxic conditioning protocols and adequate patient selection.

It is clear that there is a need for a solid phase III trial of HCT, firstly, for aggressive forms of MS and effectiveness of save low toxicity immunoablative conditioning for less incapacitating patients. There are several ongoing trials. A prospective, randomized, controlled multicentre trial has been already outlined in a positioning article of Saccardi et al. [83].

6.3. HCT in rheumatoid arthritis and juvenile idiopathic arthritis

Rheumatoid arthritis (RA) is affecting approximately 1% of the population. It is characterized by autoantibody production with progressive joint destruction due to the formation of an inflammatory hypertrophied synovium, erosion of the synovial cartilage and the surrounding bone [84]. Break of tolerance causes accumulation of immune effector cells, including macrophages and osteoclasts, DCs, B and T cells, especially Th17 subsets. Reduced T-cell receptor (TCR) excision circles and shortened telomeres result in a contracted TCR repertoire in both naïve and memory cells [85, 86].

An adequate control and a possibility of remission are usually limited to early-stage disease.

Pilot studies of HCT in RA date back to middle 1990s of the 20th century. It was shown that sustained remission responses were shortly activated for up to 6–12 months, which was followed by reintroduction of DMARDs/anti-TNF therapy. Following HCT, there was a somewhat better response to DMARDs supporting the immunomodulating effect of HCT. There has been variable success of HCT in RA, but the results have not been encouraging as compared to diseases like SSc or MS [87–89].

Published data from the EBMT registry showed no transplant-related mortality of RA patients with OS 98%, while in JIA patients, TRM was detected in 7 of 65 patients [90].

At present, HCT for RA or JRA, in general, cannot be recommended, and can be considered very seriously only in context of RA/JRA oriented well-established clinical trials.

6.4. HCT in systemic lupus erythematosus

SLE is a prototype autoimmune disease with prevalence of 20–150 cases per 100,000 populations. It is characterized by wide abundance of self-reactive antibodies, including those against nuclear and cytoplasmic antigens, as well as autoimmune activity associated with complement activation [91]. A typical characteristic of SLE is an extremely variable clinical manifestation that can make the diagnosis difficult and late.

The plasma cells are key players in pathogenesis of SLE. The immunological hallmarks of the disease are short-lived (HLA-DRhigh) plasmablasts, which are easily detectable in the circulation during active disease [92]; the upregulation of IFN-regulated gene transcripts, therefore IFN-α and its response proteins IP-10 and Siglec-1, are established markers for monitoring disease activity in SLE [93, 94]; finally, circulating Foxp3+ Tregs, especially Helios+ subpopulation, are associated with disease activity [95].

Major visceral involvement and persistent disease activities are predictors of poor outcome [96].

Treatment response varies in population subsets owing to the genetic composition and racial differences, as well as hormonal influences in both the adult and pediatric patients [97].

Immunosuppressive therapy is often protracted for adequate disease control and to minimize organ damage in patients with very high disease activity, but prolonged uses of corticosteroids and repeated courses of higher doses of immunosuppressant have resulted in unfavorable long-term disease-free outcomes or drug-free intervals [98].

Results of autologous HCT are less consistent. In an American trial by Burt et al. [99], reduced intensity HCT (Cy-ATG) in refractory SLE showed significant advantages of HCT in terms of progression-free survival and attenuation of nephritic symptoms in patients with SLE. The study (n = 50) showed promising results with respect to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score and such activity markers as ANA, anti-dsDNA and complement with increasing 5 year progression-free survival. There was either stabilization or reversal of organ dysfunction, including renal function. With a mean follow-up of 29 months, the 5 year probability of overall survival and disease-free survival (DFS) following HCT was 84 and 50%. TRM was 2% (1/50).

In EBMT too, positive trends in progression-free and overall survival were noted but the numbers are less encouraging [44, 90, 100]. The last analysis of 28 patients, transplanted between 2001 and 2008 in eight centers of six countries, using a spectrum of conditioning protocols and with median follow-up of 38 months after transplantation, demonstrated that the 5 year overall survival was 81 ± 8%, disease-free survival was 29 ± 9%, and non-relapse mortality (NRM) was 15 ± 7%. OS tended to be lower when using intermediate as compared to low-intensity conditioning ($p = 0.08$). OS was not significantly associated with the presence of renal, neurologic or hematologic involvement or of SLEDAI >20 before ASCT, anti-dsDNA antibodies at mobilization or ex vivo graft manipulation.

http://dx.doi.org/10.5772/67604

The 3 year NRM was 0% in the low-intensity conditioning versus 23 ± 10% in the intermediate-intensity conditioning (p = 0.13). It is interesting that DFS and relapse incidence were not associated with any immediate pretransplant variables, including the use of low versus intermediate conditioning regimens.

A follow-up study using third-generation "rituximab sandwich" conditioning regimen (CyATG + rituximab, a B cell targeted anti-CD20 monoclonal antibody) is ongoing [101].

6.5. HCT for Crohn's disease

Crohn's disease is a relapsing inflammatory disease, mainly affecting the gastrointestinal tract, and frequently is presented with abdominal pain, fever and clinical signs of bowel obstruction or diarrhoea with passage of blood or mucus, or both. It represents one of two major forms of IBD [102].

It is thought that the disease develops due to abnormal mucosal immune responses to the gut flora. GWAS identified >100 susceptibility loci to Crohn's disease in Caucasians but their heritability is not fully explained [103, 104]. Recent studies revealed an altered local and circulating T-cell phenotype, in particular involvement of Th17 cells and IL-21/IL-22-producing CD4+ T cells [105, 106].

Initially, it was a clear impression that HCT is an effective approach. After a few cases or small series reports [107–111], the important publication of Chicago group appeared in Blood, 2010 [112] and demonstrated that in all 25 patients, who received CyATG with autologous stem cell, the risk to develop clinical remission with Crohn's disease activity index (CDAI) < 150 (inclusion criteria CDAI > 250) was open. Relapse-free survival was 91, 63, 57, 39 and 39% at 1st, 2nd, 3rd, 4th and 5th year, respectively. Five years after transplantation, 70% of patients were in remission, 80% were steroid free and 60% medication free. There was no treatment-related mortality. In line with other cell therapies, the non-myeloablative transplantation was considered as the best studied/investigated idea of Crohn's disease treatment [102].

The EBMT paper came out in 2015 [113], presenting a parallel-group randomized clinical trial conducted in 11 European transplant units (Autologous Stem Cell Transplantation International Crohn Disease—ASTIC—trial); the medial follow-up was 1 year. Comparison of immunoablation, with use of the similar CyATG protocol and HCT (n = 23) and control treatment (n = 22), demonstrated no statistically significant in-between group differences in proportions of patients achieving sustained disease remission, with CDAI less than 150 in the last 3 months, or free of active disease. There was a statistically significant difference among patients able to discontinue active treatment in the last 3 months. There were 76 serious adverse events in patients undergoing HCT versus 38 in controls; 1 patient from HCT group died 20 days after the start of conditioning with postmortem evidence of sinusoidal obstructive syndrome (SOS). Whether the SOS, seen in the patient who died, may be an agonal event in a septic patient with development of a fulminant liver failure, or it can be a result of endothelial injury induced by high dose cyclophosphamide, is still open for discussion.

Therefore, evaluation of presented experience of HCT for refractory Crohn's disease is not straightforward; it makes further study highly necessary and strongly recommended.

6.6. HCT in other autoimmune diseases

In accordance with the EBMT data for December 2016, from 2227 reported HCT for autoimmune diseases (exact numbers not yet published), the cumulative percent of afore-discussed five conditions (SSc, MS, SLE, RA with JIA, and Crohn's disease) is 83% (data not yet published). All cases of application of transplantation for other multiple autoimmune diseases are outnumbered. There are published reports giving some evidence that transplantation might be an effective treatment option in case of severe primary systemic vasculitis. For example, in 15 transplanted patients of different forms of vasculitis with an overall response rate of 93% (46% complete), partial responses were observed [114]. HCT has been promoted in polymyositis/dermatomyositis, Sjogren's syndrome, psoriatic arthritis and ankylosing arthritis, chronic inflammatory demyelinating polyneuropathy and autoimmune cytopenias, including hemolytic anemia, ITP, Evans syndrome and other rare combinations [115, 116]. Promising preliminary results were registered in small groups of patients with type 1 diabetes (T1D) from Brazil [117, 118], China [119, 120], and Poland [121]. Preliminary lessons from these small trials suggest that: (i) majority of patients can reach independence of exogenous insulin for a period of few months to years; (ii) according to our knowledge, there were no described transplant-related deaths; and (iii) diabetic ketoacidosis at onset, probably due to a severe depletion of islet cells, can be a poor predicting factor.

However, the experience with almost all autoimmune diseases, plus some others, recently included into clinical trials, is limited to allow any generally accepted conclusions.

7. Conclusion

HCT treatment has revolutionized the approach to autoimmune diseases treatment.

The results vary with different diseases, and there is certainly a special room for well designed clinical trials. Late results sometimes also provide surprises, tending to review the initial concept. Does that mean that the existing data are not enough to make a decision-concerning transplantation, either a more positive one (for instance MS) or a more negative one (e.g., RA)? Specific issues vary significantly depending on the country's social and economic climate, differences in medical system or medical insurance barriers, and legislation requiring third-party payers, and as a result, a large portion of patients cannot afford the best, or even equivalent "conventional" lifelong treatment. The majority of failures come in the form of TRM, as well as nonresponsiveness and high relapse rate [121]. The attempts to decrease the treatment toxicity, without sacrificing the efficiency, are directed to balancing the failure-to-benefit ratio. Different conditioning protocols may be more appropriate at various stages of the disease, such as RRMS with EDSS <6 versus SPMS with EDSS > 6. However, the questions are still widely open for a profound discussion, because in many cases, the efficiency itself remains unclear (e.g., Crohn's disease). Despite a sufficient number of open issues, the number of treated patients with very promising results, especially concerning SSc and MS published in major publications in peer-reviewed prestige journals, already allow us to consider HCT, a relevant clinical option, for a successful treatment of certain autoimmune diseases.

http://dx.doi.org/10.5772/67604

Acknowledgements

The authors would wish to extend the highest appreciation and thankfulness to their colleagues from the working groups in the following institutions, where they have done major part of their research in the field of autoimmunity: University Hospital Hadassah (Jerusalem, Israel), University Hospital Sheba (Tel HaShomer, Tel Aviv, Israel), University Hospital Radium (Inst. Cancer Research, Oslo, Norway), University Hospital St. Marina (Varna, Bulgaria), University Hospital St., Anna (Varna, Bulgaria) and Medical University of Varna (Bulgaria).

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